Abdominal and pelvic tumours in children

Emma Sidebotham

Abstract

While all childhood cancers are rare, the abdomen and pelvis are common sites of origin. After haematological malignancies and intracranial tumours, neuroblastoma is the most common childhood cancer, most often arising in the adrenal gland. The next most common extracranial tumours are Wilms tumour, arising in the kidney (nephroblastoma) and rhabdomyosarcoma that may arise in a variety of sites, typically in the pelvis. Hepatoblastoma, non-Hodgkin lymphoma and germ cell tumours are other abdominal and pelvic tumours seen in childhood. Many childhood tumours appear to arise from residual embryonic cells which make them sensitive to chemotherapy and radiotherapy. Surgery plays a crucial role both in establishing the diagnosis and, in the majority of cases, by resection of the tumour.

Keywords Chemotherapy; hepatoblastoma; neuroblastoma; non-Hodgkin lymphoma; radiotherapy; rhabdomyosarcoma; sacrococcygeal teratoma; Wilms tumour

The abdomen and pelvis are common sites of origin of childhood cancers. After haematological malignancies and intracranial tumours, neuroblastoma is the most common childhood cancer, followed by Wilms tumour (nephroblastoma) and rhabdomyosarcoma.

The outcome of childhood cancers has improved dramatically in recent decades with a multimodality approach to treatment, utilizing surgery, chemotherapy and radiotherapy via clinical trials under the auspices of the Children's Cancer and Leukaemia Group (CCLG), International Society for Paediatric Oncology (SIOP) and the Children's Oncology Group (COG). Despite this, 20% of children and adolescents diagnosed with cancer will still die of their disease. Nonetheless, the outcomes for some patients are now so good that the focus of trials for low-risk disease has shifted to reducing therapy to minimize late effects: 60% of survivors will develop at least one chronic condition related to their previous treatment such as cardiomyopathy, hearing loss, cognitive dysfunction, skeletal growth restriction, infertility, hypothyroidism or secondary malignancies, and up to 25% of these may be severely disabling.

Adrenal gland

Neuroblastoma is the most common extracranial solid tumour of childhood. With an incidence of 9.5 per million children it accounts for 7.8% of all childhood cancers and around 15% of all paediatric cancer related mortality. Neuroblastomas arise anywhere within the sympathetic nervous system, 65% are adrenal in origin.

Emma Sidebotham *MBChB (Hons), MD, FRCs (Paed Surg) is a Consultant Paediatric Surgeon at Leeds General Infirmary, Leeds, UK. Conflict of interest: none.*

Rarer adrenal tumours in childhood include phaeochromocytomas, arising in the adrenal medulla, and adenomas and carcinomas arising from the adrenal cortex. These tumours typically present with symptoms of hypersecretion of hormones. Hence phaeochromocytomas cause hypertension and other symptoms of increased adrenalin secretion, whereas adrenal cortical tumours may present with symptoms of Cushing disease or virilization/precocious puberty. At least 10% of childhood phaeochromocytomas are associated with clearly defined hereditary syndromes such as multiple endocrine neoplasia type II (MEN). Of the remaining sporadic cases, at least 25% will be demonstrated to have new gene mutations and these patients should be referred for genetic assessment.

Neuroblastoma

Neuroblastoma is a small round blue cell tumour that arises from cells of neural crest origin. At least 80% of neuroblastomas arise within the abdomen, 65% within the adrenal gland, but they may develop anywhere along the sympathetic chain in the neck, chest or abdomen; 85% of neuroblastomas occur in children under 4 years of age. Its aetiology is unclear. Familial occurrence is rare.

The clinical presentation is varied and often vague. It may present with a mass at the site of origin but more frequently with symptoms of metastatic disease such as bone pain due to bone metastases or anaemia and bruising secondary to extensive bone marrow involvement. Paraspinal tumours may grow through the vertebral foramina causing symptoms of spinal cord compression. Classic but rare manifestations include periorbital bruising 'raccoon eyes' due to orbital involvement, skin invasion causing subcutaneous nodules known as 'blueberry muffin' lesions or opsoclonus–myoclonus, a paraneoplastic syndrome where children have symptoms of rapid bursts of chaotic eye movements, irregular jerking movements and ataxia.

Diagnosis of neuroblastoma is made by biopsy of the tumour: current treatment planning requiring sufficient tissue for biological studies crucial for risk stratification of disease in addition to histological diagnosis. Cross-sectional imaging of the neck, chest and abdomen is used to assess local tumour extent and metastatic disease. The overall drive is towards utilizing MRI rather than CT where possible for imaging all paediatric malignancies, to reduce the radiation burden of recurrent assessments. Calcification is seen within 90% of tumours and is strongly suggestive of the diagnosis of neuroblastoma. All children should have two site bone marrow aspirates and trephines. Elevated urinary catecholamine metabolites (homovanillic acid [HVA] and vanillylmandelic acid [VMA]) are useful in diagnosis and for monitoring response to therapy and recurrence. I^{131} metaiodobenzylguanadine (MIBG) is a radiolabelled derivative of noradrenalin that is taken up by neuroblastoma tissue at primary and metastatic sites in the majority (90%) of cases of neuroblastoma. It is useful for detecting occult metastatic disease, response to therapy and recurrence (Figure 1). PET-CT is used for none MIBG avid disease but is less sensitive.

Historically, several staging systems for neuroblastoma were in use around the world, which led to difficulties comparing different trials. Furthermore a variety of biological factors (MYCN amplification, 11q aberrations, DNA ploidy) have become apparent as relevant to prognosis. This has resulted in development of the International Neuroblastoma Risk Group

Staging System (INRGSS) based on radiological features (image defined risk factors), and a comprehensive risk stratification system of clinical (patient age, tumour stage) and biological variables, all of which are independent prognostic variables of disease progression (Table 1). This gives rise to four risk groups, very low, low, intermediate and high, with 16 subgroups (A-R). The new staging system will facilitate international collaboration and development of improved treatment regimens and novel therapies to minimize morbidity in low-risk patients and improve outcomes for high-risk groups.

Increasingly biological markers are being studied as ways of categorizing disease and stratifying treatment. Approximately 30% of neuroblastomas show amplification of the MYCN oncogene (>10 copies): overall these patients have rapid disease progression with 90% dying regardless of therapy, denoting MYCN amplified disease as high risk. The DNA index refers to the amount of DNA within the nucleus of the cell compared with the expected amount. Hyperdiploidy (DNA index>1) has been shown to correlate with a better response to chemotherapy, lower stage disease at presentation and better overall outcomes. A variety of other potential biological markers are being investigated and the INRG classification system can evolve to incorporate these when they are demonstrated to have a clear and independent role in influencing outcome and are thus of use in treatment stratification.

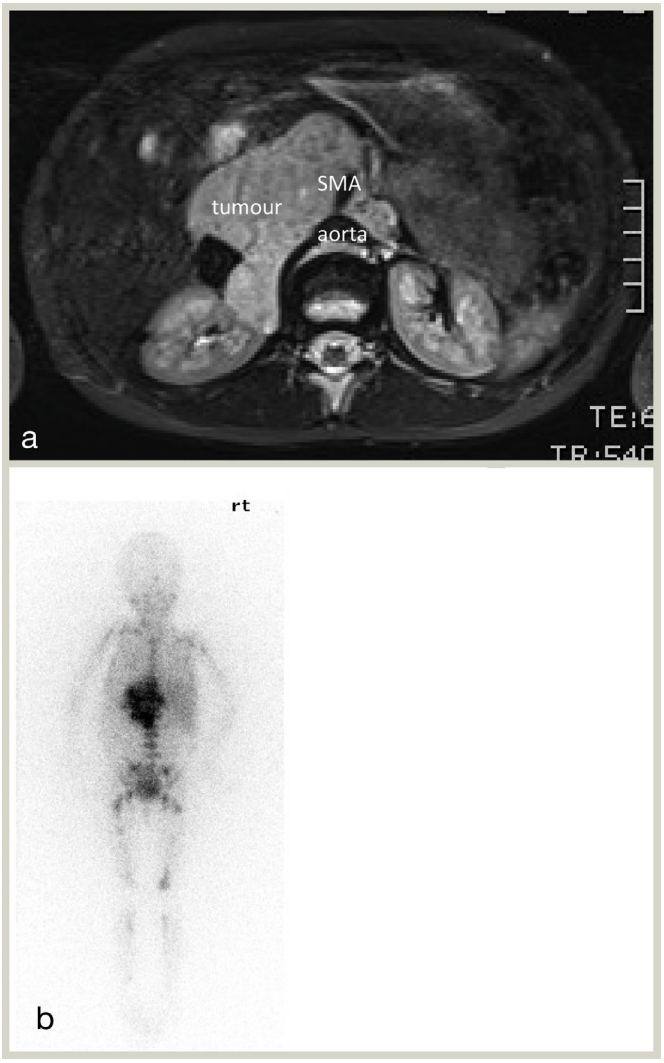

Figure 1 (**a**) MRI scan showing neuroblastoma, arising from the right paraspinal region, encasing the aorta and superior mesenteric artery (SMA). (**b**) MIBG scan (posterior view) demonstrating a left adrenal neuroblastoma and extensive metastatic disease in the bone and bone marrow. MIBG is excreted in the urine hence the bladder is also strongly positive on the scan.

Low-risk neuroblastoma may be treated by surgery alone with excellent cure rates. Tumours with no image-defined risk factors (surgical risk factors) may undergo primary resection, whereas tumours with image-defined risk factors (e.g. vessel encasement) will benefit from preoperative chemotherapy to decrease surgical morbidity. Even incompletely resected low-risk disease is considered to require no further treatment only close monitoring. Chemotherapy is indicated only for recurrence or residual symptomatic disease (e.g. cord compression symptoms).

Surgery and chemotherapy, with agents including vincristine, carboplatin, etoposide cyclophosphamide and cisplatin (COJEC), are the mainstay of treatment for intermediate risk neuroblastoma. Preoperative chemotherapy is given to try to shrink the tumour and decrease its vascularity prior to resection which aims to remove the tumour with clear margins but without damage to adjacent structures.

High-risk neuroblastomas include all MYCN amplified and metastatic disease, except the specialist subgroup MS of restricted metastatic disease (liver, skin, bone marrow [<10%]) and favourable biology in patients less than 18 months old, which has a more favourable prognosis. Treatment of high-risk neuroblastoma is multimodality. Patients receive high-dose chemotherapy prior to surgery. Tumours grow encasing surrounding vessels and structures, including the aorta and IVC, making surgical resection very challenging (Figure 1). The benefits of surgical resection of stage three, and especially stage four high-risk tumours, remain controversial. There is some good evidence to suggest that >90% resection is as effective as complete resection with less morbidity when performed as part of multimodality treatment, this applies particularly to stage four disease where the morbidity resulting from near total resection (e.g. damage to major vessels or adjacent organs) is liable to outweigh any benefit. Surgery is followed by further high-dose chemotherapy with bone marrow ablation and stem cell rescue. Retinoic acid, to encourage cell maturation, immunotherapy with antibodies to GD-2, highly expressed on neuroblastoma cells, and radioactive MIBG are then used to eliminate minimal residual disease and consolidate remission.

Localized neuroblastomas detected on fetal or neonatal imaging form a special subgroup that tend to regress spontaneously and can simply be monitored. Non-MYCN-amplified MS tumours can similarly be managed expectantly though occasionally local symptoms, for example, liver disease causing significant enlargement with systemic compromize, require treatment to ameliorate these effects.

Neuroblastoma continues to carry a bleak prognosis. Low and intermediate risk tumours carry an excellent prognosis approaching 90% survival. Unfortunately the majority of patients present with high-risk disease with survival at most 60% for children under 5 years of age but only 30% for older children. Progress in the genetic assessment of disease is likely to play a

International neuroblastoma research group risk classification

INRG stage	Age (months)	Histologic category	Grade of tumour differentiation	MYCN	11q aberration	Ploidy	Pretreatment risk group
L1/2		GN maturing; GNB intermixed					A: very low
L1		Any except GN maturing or GNB intermixed		Not amplified			B: very low
				Amplified			K: high
L2	<18	Any except GN maturing or GNB intermixed		Not amplified	No		D: low
	≥18				Yes		G: intermediate
		GNB nodular; neuroblastoma	Differentiating		No		
					Yes		E: low
			Poorly differentiating or undifferentiated	Not amplified	Yes		H: intermediate
							H: intermediate
							N: high
				Not amplified			
				Amplified			
M	<18	Any except GN maturing or GNB intermixed		Not amplified		Hyperdiploid	F: Low
	<12					Diploid	I: intermediate
	12–<18			Not amplified		Diploid	J: intermediate
	<18						O: high
	≥18			Not amplified			P: high
				Amplified			
MS	<18	Any except GN maturing or GNB intermixed		Not amplified	No		C: very low
					Yes		Q: high
							R: high
				Amplified			

GN, ganglioneuroma; GNB, ganglioneuroblastoma. Adapted from Cohn et al.

Table 1

significant role in future treatment. Relapsed disease tends to demonstrate increases in segmental chromosomal aberrations and gene mutations. Defining the genetics will allow treatment to be modified relative to risk, both reducing treatment in low-risk disease to reduce side effects and escalating treatment for high-risk disease. It will also provide the basis for the development of specifically targeted therapies to these gene pathways.

Urinary tract

Kidney

Wilms tumour is the most common renal tumour of childhood and the second most common abdominal tumour accounting for 6–10% of cases of childhood cancer. Mesoblastic nephroma, clear cell sarcoma and rhabdoid tumours are rarer childhood tumours involving the kidney. Renal cell carcinoma may occasionally arise in childhood, typically in adolescence, when it is more common than Wilms tumour.

Wilms tumour has an incidence of 7.6 cases per million children. Ten per cent of cases are associated with recognized syndromes such as hemihypertrophy, aniridia, WAGR (Wilms, aniridia, genitourinary malformations, mental retardation), Denys-Drash syndrome (nephropathy, renal failure, male pseudohermaphroditism) and Beckwith-Wiedemann (macroglossia, hyperinsulinaemia hypoglycaemia of infancy, exomphalos, visceromegaly). The propensity to Wilms tumour development in all these syndromes stems from the Wilms tumour suppressor genes (WT1 and WT2) on the short arm of chromosome 11 (Ch11p13 and Ch11p15). A further 1–2% of cases of Wilms tumours are familial and this risk is associated with the familial Wilms tumour genes FWT1 and FWT2 on chromosome 17q and 19q, respectively. Three- monthly screening ultrasounds up to the age of 8 years are advocated in these high-risk groups, including the liver in Beckwith Wiedemann up to age 4 years, due to increased risk of hepatoblastoma.

Wilms tumours classically present as a visible or palpable flank mass without other symptoms. Painless haematuria (10%), abdominal pain, occasionally acute due to tumour rupture, or symptoms of hypertension are rarer presentations. Imaging by ultrasound, MRI and CT scanning is used to clarify the nature of the mass, local invasion, vascular extension along the renal vein or IVC and metastatic disease, typically to the lungs (Figure 2).

Histologically, Wilms tumours are triphasic embryonal neoplasms. Histological subtype, together with the stage of the tumour, are crucial to determining treatment as certain subtypes, particularly diffuse anaplasia, are associated with a poor

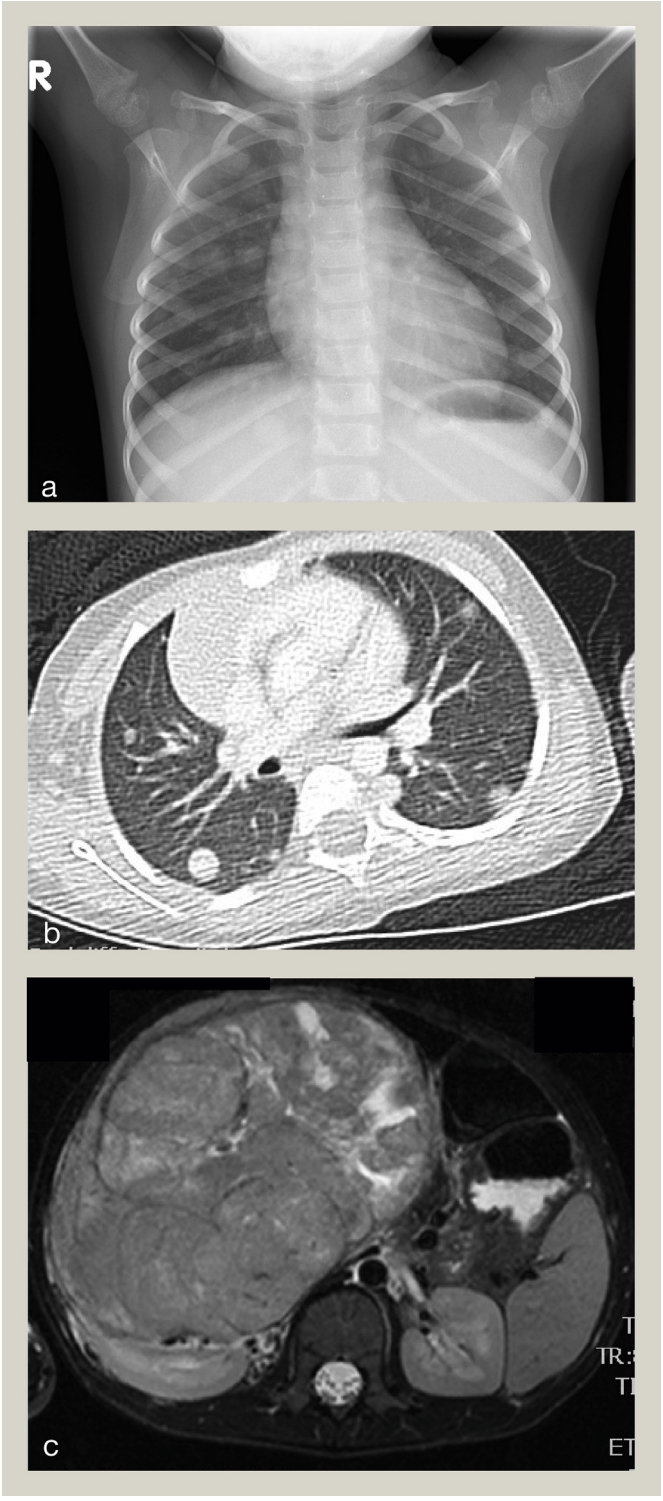

Figure 2 Wilms tumour metastases to the lung seen on chest X-ray (**a**) and CT scan (**b**) and MRI of Wilms tumour arising in right kidney (**c**).

prognosis. Histology may also show foci of disordered development, nephrogenic rests, distant to the tumour in up to one third of nephrectomy specimens, which may have the potential to develop into future tumours.

European treatment protocols (SIOP and CCLG) advocate neoadjuvant chemotherapy to shrink the tumour prior to nephrectomy then further chemotherapy as indicated by stage and histology. In the UK, a needle core biopsy is performed to confirm the diagnosis of Wilms tumour prior to initiating chemotherapy (open biopsy is considered to upstage the tumour to stage III). The North American protocols favour immediate nephrectomy followed by chemotherapy, other than where surgery is considered too high risk, intraoperative rupture/tumour spill significantly up staging the tumour with consequent intensification of treatment. Bilateral Wilms tumours (stage V) require a nephron-sparing partial nephrectomy following neoadjuvant chemotherapy. Surgery aims to remove the affected kidney and ureter, assess for tumour spread and sample lymph nodes (7+ optimal). Chemotherapy regimens are based around vincristine and actinomycin D with additional agents for more intensive regimens. Stage III and IV disease also receive renal bed and lung radiotherapy (Table 2).

Both minimally invasive nephrectomy and partial/nephron-sparing nephrectomy are widely practised for adult renal tumours. The large size of Wilms tumours and the presence of nephrogenic rests distant to the site of primary tumour make these approaches more difficult in paediatric tumour resection. Nonetheless, these approaches are being utilized in a small minority of Wilms tumours. Early reviews of minimally invasive nephrectomy found that tumour resection could be performed safely but lymph node sampling was inadequate, potentially understaging tumours. Studies reviewing nephron sparing surgery have found it to be only considered feasible in a minority of patients but where performed survival outcomes are similar to equivalent patients having a total nephrectomy. Positive resection margins were common

SIOP and UKCCLG wilms tumour staging system

Stage	Description
I	Tumour limited to kidney - completely excised
II	Tumour beyond capsule of kidney - completely excised • Capsular invasion: perirenal/perihilar • Invasion of extrarenal vessels • Invasion of ureter • Regional lymph node involvement (Stagel IN1)
III	Invasion beyond the capsule with incomplete excision • Preoperative/perioperative rupture • Peritoneal metastases • Paraaortic lymph node involvement • Incomplete excision/positive surgical margin at histology • Tumour thrombus at resection margin of vessel or ureter • Open tumour biopsy (not percutaneous)
IV	Distant metastases • Haematogenous to lung, liver, bone, brain • Lymph node metastases outside abdomen and pelvis
V	Bilateral renal tumours

Table 2

(up to one third) requiring intensified treatment on a stage III protocol, which would make long-term benefits questionable since the effects of abdominal radiation are the most significant factor in subsequent progression to end stage renal disease. Technical operative advances such as intraoperative ultrasound and haemostatic agents to allow resection through the renal parenchyma have been crucial to these developments.

Favourable histology stage I Wilms tumours have an excellent prognosis with overall 98% survival at 4 years. Even stage IV disease has a 4-year overall survival of 81% in the latest studies. Anaplastic histology carries a significantly worse prognosis with 4-year survival of only 33% for stage IV anaplastic tumours.

Chronic renal failure is rare following treatment for Wilms tumour (0.7% risk of end-stage renal disease 20 years post nephrectomy), unless associated with underlying syndromes such as Denys-Drash, but affects at least 5–12% of patients with bilateral disease long term. Late effects of chemotherapy and radiotherapy include secondary malignancies and cardiac dysfunction, hence the emphasis of recent trials to try to reduce therapy for low-risk disease. Advances in our understanding of tumour biology and the factors that influence outcome beyond the current staging systems will be crucial to the further stratification of treatment, intensifying treatments for factors noted to be associated with poorer outcomes, for example, loss of heterozygosity at chromosome 1p and 16q is a marker for intensified treatment in the latest COG protocols. To date progress in this area has been much slower than for neuroblastoma.

Bladder/prostate/vagina/uterus

Rhabdomyosarcoma

Rhabdomyosarcomas are the third most common extracranial solid tumour of childhood (4.3 per million children), and the most common pelvic malignancy. Despite histological features of aberrant skeletal muscle differentiation, rhabdomyosarcomas occur at sites distant to skeletal muscle, e.g. biliary tree, urogenital system and are believed to arise from undifferentiated mesodermal tissue. Most common are head and neck tumours followed by genitourinary rhabdomyosarcomas which account for approximately 26%.

Rhabdomyosarcomas have a bimodal pattern of occurrence, most commonly affecting children age 2–5 years with a further peak around 15–19 years of age; 40% of all rhabdomyosarcomas develop in adulthood. Most are sporadic but there are associations with Beckwith-Weidemann syndrome and Li Fraumeni syndrome, a familial cancer syndrome affecting the p53 tumour suppressor gene.

Rhabdomyosarcomas belong to the family of small round blue cell tumours. Most paediatric tumours fall into two histological subtypes, alveolar and embryonal. Embryonal histology predominates in children under the age of 10, whereas alveolar histology, which carries a much worse prognosis, predominates in adolescence. The vast majority of alveolar rhabdomyosarcomas have translocations that unite the FOX01 transcription factor on chromosome 13q with either the PAX3 or PAX7 transcription factors, fusion positive rhabdomyosarcoma. Recent studies suggest that treatment classification based on fusion positive or negative status may be a more effective way to stratify treatment than traditional histology.

Symptoms tend to be site specific either with an obvious mass or due to compression of adjacent structures. Bladder and prostate tumours produce urinary symptoms such as haematuria, frequency or retention and constipation. Vaginal tumours cause bleeding, discharge or a visible mass, like a 'bunch of grapes', botyroid tumours. Paratesticular tumours typically present as a mass in the scrotum or the groin. Fifteen per cent of rhabdomyosarcomas present with metastatic disease and these carry a poor prognosis. There is an increasing recognition of the systemic nature of high-risk rhabdomyosarcoma with spread to non-imaging apparent sites such as lymph nodes at presentation acting as reservoirs of disease for relapse. Lymph node sampling is an important part of surgical management in higher risk subtypes.

Diagnosis is made by biopsy with sufficient tissue to perform biological studies. Imaging by ultrasound, CT and MRI is used to assess both the local disease extent and distant metastases. Bone marrow aspirates and bone scans are indicated to assess distant metastases. PET-CT is likely to play an increasing role in looking for residual and metastatic disease. Tumours are finally classified into low, intermediate and high-risk groups dependent on a stage (TNM type classification for location, size, spread) and group (histological subtype and fusion protein status).

Treatment is multimodality with surgery, chemotherapy and radiotherapy. Surgery aims to achieve wide local tumour excision with uninvolved margins while preserving cosmesis and function. Chemotherapy regimens are based on vincristine, actinomycin-D and ifosfamide/cyclophosphamide (Europe/North America) but new agents such as irenotecan and topotecan have been introduced to try to improve outcomes in high-risk disease where prognosis remains poor.

In the past, bladder and prostate rhabdomyosarcomas was managed by pelvic exenteration, formation of an ileal conduit for urinary diversion and frequently a permanent colostomy. This has reduced with modern multimodality treatment regimens but 30–40% of these patients will still loose their bladder in order to effect a cure. The effects of pelvic radiotherapy in small children can be very disabling, limiting doses given. European protocols have tended to limit treatment, especially radiotherapy, to reduce treatment side effects with consequent higher relapse rates, generally salvageable with treatment escalation.

Vaginal tumours typically affect young children (<5 years), have a botyroid or embryonal histology and tend to carry an excellent prognosis. These initially were also treated by pelvic exenteration but current treatment is predominantly with biopsy then chemotherapy with excellent prognosis without need for significant surgical resection. Uterine rhabdomyosarcomas typically occur in older patients (>12 years), they have a poorer prognosis and tendency to local recurrence but modern treatment regimens with neoadjuvant chemotherapy has decreased the extent of surgical resection required while maintaining good cure rates.

Overall survival rates for rhabdomyosarcoma treated with current combination therapy regimens are more than 60%. Prognosis is related to disease risk; low-risk tumours have greater than 90% 5-year survival, intermediate risk 55–70% and high risk less than 50%. Reducing side effects while curing low-risk disease has been the major progress and outcomes for high-risk tumours have not improved in the last 50 years.

Liver

Primary liver tumours are rare in childhood accounting for less than 2% of all paediatric malignancies. Of these, 80% are hepatoblastoma with an incidence of around one per million children. Hepatocellular carcinoma (HCC) occurs in older children, median age of 11 years. Congenital metabolic and inflammatory diseases of the liver predispose to HCC and a third of patients will have cirrhotic disease of the liver which limits radical resection as a treatment option. Five-year survival rates are dismal at 17–28%.

Hepatoblastoma

Hepatoblastoma is an embryonal liver tumour that occurs almost exclusively in children under 3 years of age. Its incidence has increased in recent years probably explained by the increased risk in very low birth weight infants, though the cause of their increased risk remains uncertain. Several syndromes are also associated with an increased incidence of hepatoblastoma including Beckwith-Weidemann and familial adenomatous polyposis.

Like many childhood tumours, hepatoblastoma frequently presents as an asymptomatic mass. There may be associated fever, lethargy and anorexia. Jaundice is rarely a feature. Hepatoblastoma is typically associated with an elevated alpha fetoprotein (AFP) level (>90%). Some benign liver tumours such as mesenchymal hamartomas may also have an elevated AFP. Elevated AFP can be difficult to interpret in young infants where levels are naturally high at birth and progressively fall over the first year of life.

Hepatoblastoma has characteristic features on imaging. Ultrasound is useful to assess the liver and vessel involvement. Cross sectional imaging by CT or MRI is essential to look for metastatic disease, which occurs most commonly to the lungs.

Biopsy will establish a definite histological diagnosis. Due to the potential risks of biopsy (bleeding, tumour rupture) selected patients in some trials have been treated on the basis of age, classic imaging features and serum AFP alone.

There is a move to classify all patients using the PRETEXT (pre-treatment extent of disease) system. PRETEXT divides the liver into four regions and classifies disease based on the contiguous areas involved and tumour free. In addition to the location of disease there are a variety of sub-classifications including nodal involvement (N), vascular invasion (P and V), multifocal disease (F), extrahepatic spread (E) and distant metastases (M) (Figure 3).

Traditionally, treatment varied significantly between Europe and North America. SIOPEL (SIOP-epithelial liver) favoured neoadjuvant chemotherapy prior to surgical resection as 90% response rates can be seen, whereas the COG studies favour primary surgery for all tumours where complete resection can be achieved (stage I and II) with subsequent chemotherapy based on extent and histological subtype. Surgery aims to completely resect the tumour: a margin of only millimetres is acceptable clearance. Generally, hepatoblastomas arise in non-cirrhotic liver and resections of up to 85% of liver tissue may be tolerated. Stage IV tumours and those with portal vein involvement should be considered for treatment by orthotopic liver transplant as complete resection is impossible. Live-related donor transplant is particularly useful in this setting as it can be timed to fit in with chemotherapy regimens. A worldwide collaboration, the Childrens Hepatic Tumours International Collaboration (CHIC) has been formed, including COG, SIOPEL, Japan and South America and is launching a multinational study Paediatric Hepatic International Tumour Trial (PHITT).

Cisplatin-based regimens form the mainstay of chemotherapy for hepatoblastoma. Hearing loss is a particular problem with platinum-based chemotherapy and as for many paediatric cancers, trials aim to introduce more effective regimens for high risk tumours while reducing treatment in lower risk disease. Prolonged courses of preoperative chemotherapy should not be attempted as the development of resistance of hepatoblastoma to chemotherapy after relatively short courses is well recognized.

The overall survival rate for children with hepatoblastoma is 70%. Outcomes have improved significantly in the last few years. Limited (PRETEXT I and II) and low-risk tumours have event free survival of 80–90% and overall survival rates of 85–100%. However, outcomes for extensive or high-risk tumours continue to carry a poor prognosis with overall survival of 50–60%.

Liver metastases

Resection of liver metastases has demonstrated therapeutic and survival benefits in selected adult patients from a variety of primary tumours including colorectal carcinoma and breast cancer. Neuroblastoma is the most common childhood solid tumour to metastasize to liver (20–30%), followed by Wilms tumour (10–15%). Germ cell tumours, gastrointestinal stromal tumours, osteosarcoma, desmoplastic small round cell tumours and neuroendocrine tumours may also metastasize to liver.

Stage MS neuroblastoma is a curious subtype in children under 18 months which has the potential to resolve spontaneously but can occasionally cause massive hepatomegaly resulting in respiratory and circulatory compromise. This is best managed with chemotherapy and/or radiotherapy as surgical interventions have high morbidity and mortality. Liver metastases associated with other subtypes of neuroblastoma tend to be associated with widespread metastatic disease where liver resection is unlikely to confer benefit. Liver involvement from Wilms tumour may result from direct local invasion or metastasis and can be resected though metastatic disease to the liver overall is associated with a poor prognosis. In general paediatric solid tumours tend to be chemosensitive and as liver metastases are associated with a very poor prognosis, at present, there is little role for surgery in their treatment.

Germ cell tumours

Germ cell tumours in childhood are believed to develop from aberrant or arrested migration of common progenitor cells, with 66% of paediatric germ cell tumours arising in extragonadal sites such as the mediastinum, retroperitoneum and sacrococcygeal region whereas in adults 90–95% arise in the gonads. Teratomas contain elements from one or more of the embryonal germ layers, which is foreign to the site of origin. Typically benign, they are classified as mature or immature. Yolk sac tumours are the most common malignant germ cell tumours of infancy and childhood, metastasizing to lymph nodes and lung.

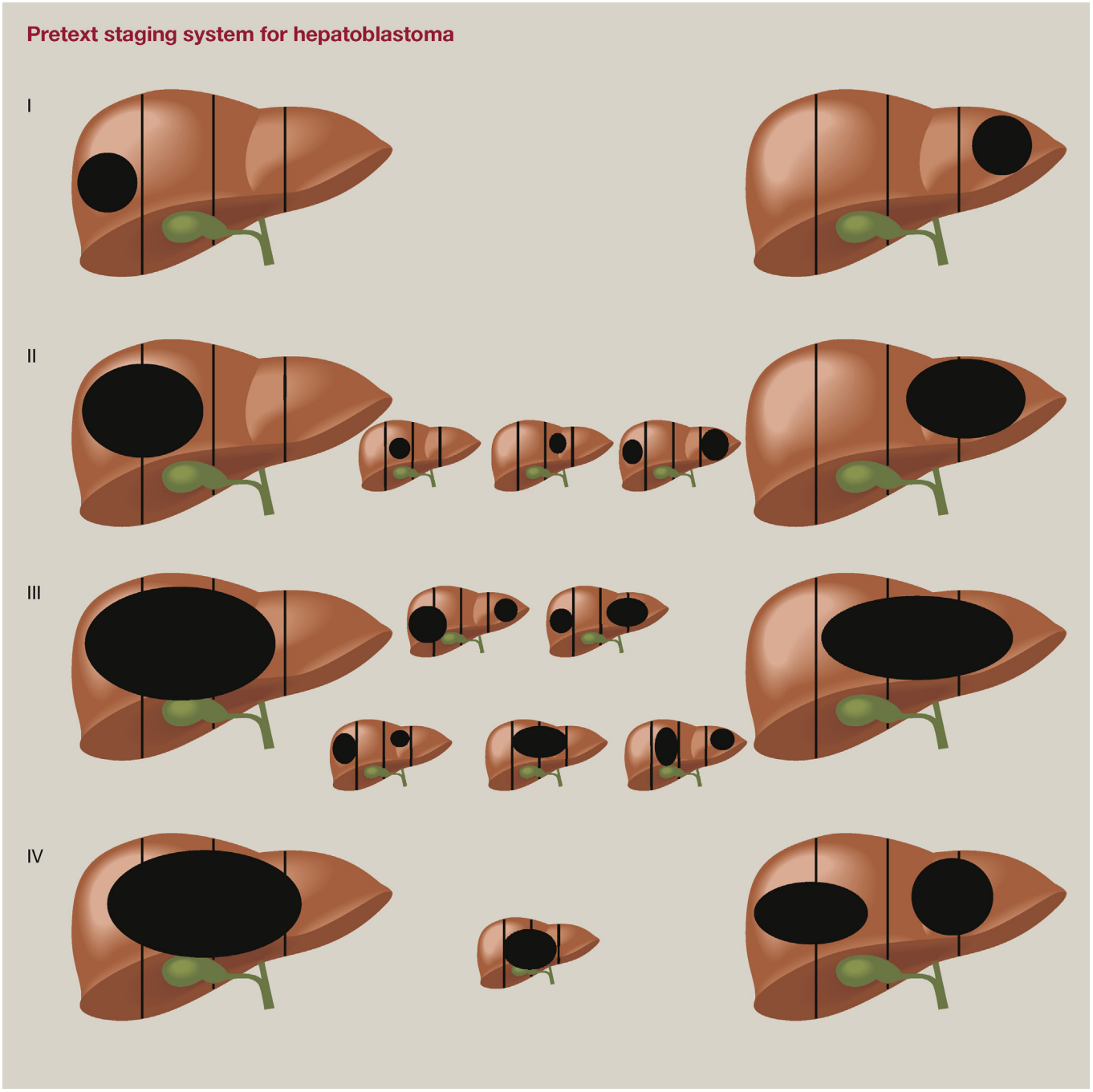

Figure 3

Serum AFP is elevated with yolk sac tumours and sacrococcygeal teratomas. Human chorionic gonadotrophin (βHCG) is elevated in choriocarcinoma. These serum markers are useful both in primary diagnosis and monitoring response to treatment, and should be measured in any patient where a germ cell tumour is suspected. Failure of the serum marker to fall or a further rise after an initial fall, are indicative of residual or recurrent disease.

Ovarian tumours occur throughout childhood. 80% of ovarian tumours are benign (epithelial cysts, teratomas); primarily solid tumours and those with raised serum markers (βHCG, AFP) have the greatest risk of malignancy. Tumours confined to the ovary and completely excised without spill are treated by surgical resection alone. Higher stage disease requires chemotherapy in addition.

Teratomas and yolk sac tumours may arise in the testis. Suspicion of a malignant process in the testis requires preoperative imaging and excision of the testis through an inguinal incision with high ligation of the spermatic cord. A scrotal approach has been shown to worsen prognosis. Completely excised tumours (stage I) are managed by excision alone with close observation. Higher stage disease is managed with surgery and chemotherapy.

Platinum-based chemotherapy regimens are highly effective at treating paediatric germ cell tumours. Stage I gonadal tumours

and all immature teratomas at any site have an excellent prognosis with surgical resection alone, followed by close monitoring. Intermediate risk tumours, stage II–IV testicular, stage II–III ovarian and stage I–II extragonadal also have an excellent prognosis with surgery and chemotherapy. Stage IV ovarian tumours (distant mets typically lung and liver) and stage III–IV extragonadal tumours have a worse prognosis requiring more intensive chemotherapy.

Sacrococcygeal teratoma

Sacrococcygeal teratoma is the most common paediatric teratoma, affecting 1 in 40,000 live births. Girls are affected much more frequently than boys (4:1). Typically benign tumours, they may develop malignant features if diagnosis is delayed or resection incomplete. Usually obvious at birth as a mass in the sacral region, the majority are now detected on antenatal scans.

Tumours typically have an intrapelvic presacral component and were classified into four subtypes by Altman:

I predominantly external (46.7%)
II external with significant intrapelvic extension (34.7%)
III visible externally but predominantly intrapelvic/intra-abdominal (8.8%)
IV entirely presacral (9.8%).

Type IV tumours frequently present late with symptoms such as constipation or urinary retention. These are at risk of developing malignant features before presentation. Currarino's Triad describes the association of a presacral mass with anal stenosis and sacral defects.

Sacrococcygeal teratomas are associated with a grossly elevated alpha-fetoprotein. AFP levels are high in all babies at birth and should drop to normal by 9 months of age; 10–15% have malignant features, which are more common in late presentation. Patients should be followed clinically and with serial AFP monitoring up to 3 years of age.

Treatment requires resection of the mass together with the tip of the coccyx. Prior to surgery the extent of intrapelvic or intra-abdominal extension should be assessed by imaging, ideally MRI. A combined approach (open or laparoscopic) is advisable for significant intrapelvic extension, to control the feeding median sacral vessel safely from above and mobilize the internal component of the tumour.

The majority of patients are cured by surgery alone, though up to 10% may get recurrent disease. Recent long term follow up studies have demonstrated many patients have problems with urinary and bowel continence persisting into adulthood due to stretching of nerves and pelvic floor from the primary mass and damage to structures during resection.

Non-Hodgkin lymphoma

Lymphoma accounts for about 6% of childhood cancers of which 60% are non-Hodgkin lymphomas. Non-Hodgkin lymphoma in childhood typically presents at extranodal sites, most commonly in the abdomen (30%).

Histologically, non-Hodgkin lymphoma is divided into four subtypes based on cell of origin and markers expressed. The most common variant in childhood is undifferentiated (40–50%), which includes Burkitt lymphoma, and accounts for the majority of abdominal disease. Lymphoblastic (30–40%) is a T-cell lymphoma, commonly found at mediastinal sites. Large cell tumours (15%) may be B or T cell, are aggressive and may arise at any site. The follicular subtype is a B-cell lymphoma seen rarely in children (<2%).

The most common site in the abdomen is the bowel, typically in the distal ileum or ascending colon. It presents with a variety of symptoms such as pain, nausea, vomiting, weight loss, fever and a palpable mass. Bowel obstruction or intussusception may result. The liver, pancreas, kidneys, ovaries or testes may also be the primary site.

Non-Hodgkin lymphoma is treated by chemotherapy determined by histology, immunophenotype and extent of disease. The role of the surgeon is to take an adequate biopsy to establish the diagnosis. Obstruction, particularly secondary to intussusception should be relieved but these tumours frequently shrink rapidly with chemotherapy and radical debulking procedures are not indicated as they are liable to delay administration of chemotherapy rather than contribute to a cure.

Stage I and II non-Hodgkin lymphoma carries an excellent prognosis, with 85–95% 5-year survival. Survival of stage III and IV tumours is influenced by histological subtype; undifferentiated/Burkitt's 75% 5-year survival, 65–75% for lymphoblastic lymphomas and 50–70% for large cell lymphomas. Outcomes for relapsed disease are poor.

Conclusion

Advances in the treatment of paediatric malignancies continue, but outcomes remain very poor for high-risk neuroblastoma and rhabdomyosarcoma and relapsed Wilms tumour. Increased international collaboration with standardized definitions and staging will allow valid trials of new treatments in small subsets of patients. Central review of histology and imaging are also optimal in ensuring correct classification of tumours for effective treatment. Advances in imaging and understanding tumour biology will play crucial roles in developing treatments and balancing cure against late effects of therapies. ◆

FURTHER READING

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- Neuroblastoma Treatment
- Wilms Tumour and Other Childhood Kidney Tumors Treatment
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